Paper No. 15

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte FABIENNE CHARELES DE LA BROUSSE AND
JIN-LONG CHEN

Appeal No. 2001-1148
Application No. 09/114,552

ON BRIEF

Before WILLIAM F. SMITH, LORIN, and SCHEINER, Administrative Patent Judges.

LORIN, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 11-15, all the claims pending in the application.[1]

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[1] Pursuant to 35 U.S.C. § 6(b), we review the adverse decision of the examiner. In doing so, we have considered the record, including:

- Final Rejection (paper no. 7);
- Brief (paper no. 9);
- Examiner's Answer (paper no. 10);
- Reply Brief (paper no. 11);
- Examiner Communication (paper no. 12);
- Second Reply Brief (paper no. 13); and,
- Second Examiner Communication (paper no. 14).

Claims 11 and 14 are illustrative of the claims on appeal and read as follows:

11. An isolated genetic knock-in primary mammalian adipocyte isolated from a transgenic mouse, wherein the adipocyte is a progeny of a genetic knock-in cell made by homologous recombination of a native ob allele with a transgene comprising a sequence encoding a reporter flanked by flanking sequences which effect, in conjunction with the cell, the homologous recombination of the transgene with the native ob allele, whereby the transgene resides on a chromosome in the transgenic mouse, wherein the expression of the reporter is under the control of native gene expression regulatory sequences of the native ob allele.

14. A cell-based method for screening for modulators of ob gene expression, the method comprising steps:

(a) determining a first reporter expression level in a first isolated mammalian adipocyte according to claim 11;

(b) contacting a second isolated mammalian adipocyte according to claim 11 with a candidate agent under conditions whereby but for the presence of the agent, the reporter is expressed at the first reporter expression level;

(c) determining a second reporter expression level in the second isolated mammalian adipocyte; and

(d) comparing the first expression level with the second expression level , wherein a difference between the first and second expression levels indicates that the candidate agent modulates ob gene expression.

The references relied upon by the examiner are:

Tartaglia U.S. 5,741,666 April 21, 1998

Kitamoto et al. (Kitamoto), "Humanized Prion Protein Knock-in Cre-Induced Site-Specific Recombination in the Mouse," Biochemical and Biophysical Research Communications, 222, 742-747 (1996).

Kress et al. (Kress), "Hox-2.3 upstream sequences mediate lacZ expression in intermediate mesoderm derivatives of transgenic mice," Development ,109, 775-786 (1990).

Halaas et al. (Halaas), "Weight-Reducing Effects of the Plasma Protein Encoded by the obese Gene," Science, Vol. 269, pp. 543-546, 28 July 1995.

Cusin et al. (Cusin), "The ob Gene and Insulin A Relationship Leading to Clues to the Understanding of Obesity," Diabetes, Vol. 44, pp. 1467-1470 (December 1995).

Capecchi, "Targeted Gene Replacement," Scientific American, Vol. 270, No. 3, pp. 34-41 (March 1994);

Sista et al. (Sista), "A cell-based reporter assay for the identification of protein kinase C activators and inhibitors," Abstract from Mol Cell Biochem, 141(2): 129-34; (1994)

Dubuc, "The development of obesity, hyperinsulinemia, and hyperglycemia in ob/ob mice," Abstract from Metabolism, 25(12):1567-74 (1976).

Claims 11-15 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kress, Kitamoto, Sista, Tartaglia, Dubuc, Halaas, Cusin, and Capecchi.

DISCUSSION

The initial burden rests with the examiner to establish a prima facie case of obviousness of the claimed invention over Kress, Kitamoto, Sista, Tartaglia, Dubuc, Halaas, Cusin, and Capecchi. See In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). "To establish a prima facie case of obviousness based on a combination of references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). We fail to find such a suggestion. Instead, we find that, through hindsight, examiner has located various elements of the claims in the prior art and pieced them together to arrive at the claimed invention.

Our discussion will focus on claim 11 as representative of the claims on appeal. All the claims on appeal depend from claim 11.

Claim 11 is directed to a genetic knock-in primary mammalian adipocyte isolated from a transgenic mouse. The claimed adipocyte is a progeny of a genetic knock-in cell. The genetic knock-in cell is made by homologous recombination of a native ob allele with a transgene; the transgene comprising a sequence encoding a reporter flanked by flanking sequences and residing on a chromosome in the transgenic mouse. According to the claimed invention, expression of the reporter is under the control of native gene expression regulatory sequences of the native ob allele and the flanking sequences effect, in conjunction with the cell, the homologous recombination of the transgene with the native ob allele.

Examiner has applied Kress, Kitamoto, Sista, Tartaglia, Dubuc, Halaas, Cusin, and Capecchi. The parties largely agree on what the references teach. In fact, appellants' (Brief, p. 6) state that "[a]pplicants readily acknowledge that all pieces of their cells, animals and methods exist in the prior art. " Accordingly, there is no dispute that each and every element of the claimed invention is disclosed in one or more of the cited references[2] and therefore we need not determine whether any particular element in the claims is taught in the prior art references. Since "identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention," In re Kotzab, 217 F. 3d 1365, 1369, 55

[2] Appellants' (Brief, p. 3) acknowledge that "[t]he Final Action aptly cites references that teach how to make transgenic animals (Capecchi), how to perform replacement (Kitamoto) and insertional (Kress) mutagenesis, the knowledge and importance of the ob gene (Dubuc, Halaas and Cusin), how to screen for drugs using a transcriptional reporter assay (Sista), how to use genes differentially expressed in obese mice (Tartaglia), and from all these pieces, constructs a reasonable facsimile of the claimed invention."

USPQ2d 1313, 1316 (Fed. Cir. 2000), the issue is whether there is "some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant," id.

The statement of the rejection in the Examiner's Answer is such that there is no primary reference, although the greater part of examiner's discussion relies on Kress, Kitamoto, Sista and Tartaglia. In our view, Tartaglia is the closest prior art. Only Tartaglia (Section. 5.2.4.2 Cell-Based Assays, cols. 30-31) discloses isolating primary adipocyte cells from transgenic mice as claimed. Also as claimed, Tartaglia introduces a transgene into the chromosome of the cell via gene targeting (col. 29, lines 42-50), which can involve "homologous recombination with chromosomal sequences" (col. 29, line 48). Furthermore, Tartaglia suggests that one way of including the transgene would be to ligate the coding portion of the transgene sequence "to a regulatory sequence which is capable of driving gene expression" (col. 28, lines 61-65). This suggests to us that, like the claimed invention, expression of the transgene sequence is under the control of gene expression regulatory sequences of a native allele.

However, Tartaglia differs significantly from the claimed invention in transfecting the adipocyte cells with "sequences capable of increasing or decreasing the amount of target gene expression within the cell" (col. 31, lines 24-27). Tartaglia does not show transfecting with a transgene comprising a sequence encoding a reporter as claimed. Tartaglia discloses only target gene sequences (col. 29, line 42) corresponding to those genes identified as being regulated by, for

example, the ob gene (col. 10, line 30), and which are differentially expressed in obese versus lean mice (col. 10, lines 33-41).

Accordingly, to meet the initial burden of establishing a prima facie case of obviousness, it is incumbent on the examiner to explain how one of ordinary skill in the art would be led to modify Tartaglia so as to produce a mouse primary adipocyte containing a chromosome on which resides a transgene comprising a sequence encoding a reporter.

Examiner relies on Kress and Sista for teaching the use of reporter genes.

Regarding Kress, examiner (Examiner's Answer, p. 5) states that it "teaches the use of promoter[3]/reporter[4] constructs to study promoter function in transgenic mice and transfected cells." However, Kress does not make a knock-in cell via homologous recombination of a native allele with a transgene containing the reporter gene. In fact, examiner (Examiner's Answer, p. 6) concedes that "Kress does not teach the targeted integration of the promoter/…transgene into the … chromosomal locus, rather chromosomal integration was random." The result of modifying Tartaglia in view of Kress is a reporter-containing construct that randomly resides on the chromosome; this is in contradistinction to the specific insertion of the reporter sequence resulting from the homologous recombination described in

[3] Examiner (Examiner's Answer, p. 5) interprets the phrase "expression regulatory sequence," set forth in the claims, as encompassing promoters. Based on that interpretation, the promoter discussed in Kress is similar to that element of the claims which requires "the expression of the reporter [to be] under the control of native gene expression regulatory sequences of the native ob allele."

the claims. Combining Tartaglia and Kress would not lead one to the claimed invention and, therefore, they are not a sufficient basis on which to establish a prima facie case of obviousness for the claimed invention.

Examiner apparently agrees because examiner looks to Kitamoto for a technique that, unlike the Kress technique, will produce a targeted rather than random integration of the reporter gene in the mouse chromosome. Examiner (Examiner's Answer, p. 8) states that

> because the site of chromosomal integration is random, a transgenic animal according to the design of Kress may suffer the drawback of position effects on gene expression from its promoter, or a deleterious mutation of a gene at the site of insertion. Targeted integration, as taught by Kitamoto, avoids these problems.

Accordingly, as best we can understand, examiner is taking the position that one of ordinary skill in the art would look to Kress for the general concept of inserting a reporter gene, notwithstanding its random integration, but then would look to Kitamoto for the more advantageous technique of targeting the insertion of Kress' reporter gene into the ob-containing mouse chromosome that Tartaglia discloses. The difficulty with this position is that we are provided no evidence of the asserted drawbacks to Kress' technique. Examiner speculates that the Kress technique "may suffer" drawbacks sufficient to warrant using the Kitamoto technique. Even if these drawbacks to the Kress technique were well known, examiner does not explain why one of ordinary skill would select the Kitamoto technique as the solution.

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[4] The reporter genes used by Kress are the luciferase gene for transfecting cells in vitro and the lacZ gene for transgenic mice. The instant claims cover similar reporter genes; see especially instant claim 13 which defines the reporter gene as being luciferase.

We can find nothing in the prior art that would lead one of ordinary skill to select Kitamoto's technique as the means for inserting Kress' reporter gene in the mouse chromosome.

We now turn to Sista which, like Kress, examiner has cited for its teaching of a reporter gene. According to the examiner[5], Sista teaches mouse fibroblast cells transfected with a construct "containing a triplet repeat of the TPA response element (TRE) upstream of a thymidine kinase promoter fused to the human growth hormone (hGH) gene" (lines 6-8). Therefore, Sista is directed to inserting a particular reporter gene within the chromosome of a mouse cell. While we recognize that Sista indicates that the mouse fibroblast cell line "has been stably transfected", how the "stably transfected" cell line has been produced is not explained. It is a matter of speculation whether Sista employed a homologous recombination technique, like the one claimed, to insert the disclosed construct in the mouse chromosome. Accordingly, Sista is relevant only to the extent that it teaches a particular reporter construct. In that regard, modifying Tartaglia in view of Sista would result in Sista's particular reporter-containing construct residing somewhere on the mouse chromosome. This combination of references, however, fails to lead one of ordinary skill to locate the construct on the chromosome such that "the expression of the

[5] Examiner (Examiner's Answer, p. 6) states that

> Sista teaches a cell-based assay for identifying modulators of gene expression. In this system, cells were stably transfected with a reporter gene operably linked to TPA response elements (TREs). TREs are DNA segments which stimulate RNA transcription in response to protein kinase C (PKC) activity, so modulation of PKC activity is reflected in modulation of reporter gene expression. The reporter gene in this assay encoded human growth hormone (hGH). Modulators of gene expression were identified by incubation of candidate compounds with cells containing the reporter construct, and subsequent measurement of hGH expression.

reporter is under the control of native gene expression regulatory sequences of the native ob allele" as claimed. Accordingly, combining Tartaglia and Sista would not lead one to the claimed invention and, therefore, they are not a sufficient basis on which to establish a prima facie case of obviousness for the claimed invention.

We recognize that each and every element that is claimed appears in one of Tartaglia, Kress, Kitamoto and/or Sista. However, the mere fact that the prior art could be modified to obtain the claimed process does not make the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Something in the prior art as a whole must suggest the desirability of isolating the claimed adipocyte from a genetic knock-in cell made by homologous recombination of a native ob allele with a transgene comprising a sequence encoding a reporter. Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984). We fail to find anything in the prior art that would lead one of ordinary skill in the art to the make the modifications discussed by the examiner.

Examiner (Examiner's Answer, p. 10) argues that "one would be motivated to combine the teachings of Tartaglia, Sista, Kitamoto, and Kress in constructing a transgenic knock-in mouse comprising a reporter gene driven by a native promoter in the natural chromosomal context." We do not agree. Looking at these four references, and in view of our earlier discussion, the best that can be said is that

these references lead one to insert a reporter gene in a mouse chromosome. There is nothing here that would guide one to use gene targeting to insert the reporter gene or to locate the reporter gene such that "the expression of the reporter is under the control of native gene expression regulatory sequences of the native ob allele" as claimed. Examiner has not pointed to anything that can be considered as giving one of ordinary skill that guidance.

The only reason we can find to use gene targeting to insert the reporter gene and to locate the reporter gene such that "the expression of the reporter is under the control of native gene expression regulatory sequences of the native ob allele" is provided by appellants' specification; that is, to accurately reflect ob gene expression in a method for screening for agents which regulate the level of ob gene expression (see specification , pp. 2-3). However, it is impermissible to use the disclosure from appellants' specification as a blueprint to reach the claimed invention from the prior art disclosure. "When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself." Uniroyal Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1051, 5 USPQ2d 1434, 1438 (Fed. Cir.), cert. denied, 118 S.Ct. 1548 (1988). Nevertheless, one cannot rely on appellants' disclosure to support a case of obviousness. Obviousness can not be established by hindsight combination to produce the claimed invention," In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). Since the only reason for employing a reporter gene as claimed is provided by the

specification, we conclude that the examiner has not met the burden of establishing a prima facie case of obviousness of the claims over Kress, Kitamoto, Sista, Tartaglia, Dubuc, Halaas, Cusin, and Capecchi.

The rejection of claims 11-15 under 35 U.S.C. § 103(a) as being unpatentable over Kress, Kitamoto, Sista, Tartaglia, Dubuc, Halaas, Cusin, and Capecchi is reversed.

REVERSED

WILLIAM F. SMITH)
Administrative Patent Judge)

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